Neurobiology of the Phenomenon of Carving

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PART 1 - PURPOSE

The Disease Concept of Addition is Still Being Questioned

• Addiction is a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences. (NIDA, 2014)

• It is considered a brain disease because drugs change the brain; they change its structure and how it works.

Need to Forge a Stronger Link

Cravings
Compulsive drug use
Drug-seeking behaviors

Neurobiology
NIH Stages of Addiction

Language of Neurobiology
(Brain Images)

PET Scans

Functional MRIs

Highly Colored

Mostly Gray
(Some Color)
Neuroimaging the Effectiveness of Substance Use Disorder Treatments

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Abstract Neuroimaging techniques to measure the function and biochemistry of the human brain such as positron emission tomography (PET), proton magnetic resonance spectroscopy (1H MRS), and functional magnetic resonance imaging (fMRI) are powerful tools for assessing neurobiological mechanisms underlying the response to treatments in substance use disorders. Here, we review the neuroimaging literature on pharmacological and behavioral treatment in substance use disorders. We focus on recent efforts of medications that reduce craving (e.g., naltrexone, bupropion), techniques that improve cognitive control (e.g., meditation, transcranial magnetic stimulation), and behavioral treatments for substance use disorders (e.g., cognitive bias modification training, virtual reality, motivational interventions) and neurochemical interventions such as neurofeedback and transcranial magnetic stimulation. A consistent finding for the effectiveness of therapeutic interventions identifies the improvement of executive control networks and the dampening of limbic activity highlighting their values as targets for therapeutic interventions in substance use disorders.

Keywords Addictive • PET - Neuroradiology - Treatment

Introduction

Addiction is a disease that cycles through states of intoxication, craving, bingeing, and withdrawal and is mainly characterized by the continuation of drug taking despite a waning of
Neurobiology-Informed Recovery

An initial fMRI study on neural correlates of prayer in members of Alcoholics Anonymous

Marc Galanter, MD, Zoran Josipovic, PhD, Helen Demetris, PhD, Jochen Weber, and Mary Alice Milardo

ABSTRACT

Background: Individuals with alcohol-use disorders who have experienced alcohol craving before joining Alcoholics Anonymous (AA) report little or no craving after becoming long-term members. Their use of AA prayer may contribute to this. Neural mechanisms underlying this process have not been delineated. Objective: To define experiential and neural correlates of diminished alcohol craving following AA prayer in members with long-term abstinence. Methods: Twenty-two members with long-term abstinence participated. Self-report measures and functional magnetic resonance imaging of differential neural response to alcohol craving-inducing images were obtained in three conditions: after reading AA prayers, after receiving intent alone, and with placebo instructions. Random-effects robust regression was computed for the main effect (prayer > placebo) and for estimating the correlations between the main effect and the self-report measures. Results: Compared to the other two conditions, the prayer condition was characterized by less self-reported craving, increased activation in left anterior middle frontal gyrus, left superior parietal lobule, bilateral precuneus, and bilateral posterior middle temporal gyrus. Craving following prayer was inversely correlated with activation in brain areas associated with salience detection and the default mode network, and with characteristics reflecting AA program involvement. Conclusion: AA members’ prayer was associated with a relative reduction in self-reported craving and with concurrent engagement of neural mechanisms that reflect control of attention and emotion. These findings suggest neural processes underlying the apparent effectiveness of AA prayer.

Introduction

Alcoholics Anonymous (AA) is an abstinence-oriented fellowship with over 2.2 million members in the United States, of which 73% report over 1 year of abstinence, and attend an average of 2.6 meetings weekly (1). Narcotics Anonymous also employs the Twelve Step approach, and meeting attendance reports an average of 6.1 years of abstinence (2).

The majority of long-term Twelve Step members who we have surveyed report no alcohol or drug craving; for AA, 79% reported no craving for alcohol (3,4), and for NA, 49% reported no craving for alcohol or drugs (2). This is notable, since people joining and persisting in attending these fellowship meetings are among the more severely addicted, having suffered from considerable craving for their principal substances of use. In fact, “craving, or a strong desire to use alcohol (or another drug)” is one of the formal criteria for diagnosing an addiction in the diagnostic manual of the American Psychiatric Association (5). Unlike other criteria, it is listed as potentially persisting, even in an addicted person in remission. In light of this, a framework based on recent neural findings can be constructed to encompass the impact of the Twelve Step experience on the recovery process (6). The elimination of craving in long-term Twelve Step members therefore merits investigation to ascertain the nature of craving, an important aspect of persistent remission.

Craving

Assessments of cue reactivity and craving have typically been conducted on subjects who are either non-treatment seeking, in a detoxification unit, or in treatment, as reflected in a recent review of 28 such studies (7). Findings in these studies illustrate how craving is...
And does not science demonstrate that visual proof is the weakest proof?

Alcoholics Anonymous (p. 48)

http://thebrain.mcgill.ca
BRAIN

The brain is made up of billions of nerve cells called neurons.

The space between two neurons is called the synapse.

Drugs of abuse act at the synapse.
• Everything in the universe is made up of tiny particles called **atoms**.

• Atoms combine to form **molecules** that are useful to man.
7,590,000,000,000,000,000,000,000 (sextillion) molecules in an 8 once glass of water

163,000,000,000,000,000,000,000,000 (quintillion) molecules in 1 gram of heroin
Origin of Heroin

Papaver somniferum

Opium

“juice of the plant”

Natural Drugs - drug molecules isolated from plants

\[
\begin{align*}
\text{morphine} & : \begin{array}{c}
\text{HO} \\
\text{O} \\
\text{H} \\
\text{N-CH}_3 \\
\text{HO} \\
\end{array} \\
\text{codeine} & : \begin{array}{c}
\text{CH}_3\text{O} \\
\text{O} \\
\text{H} \\
\text{N-CH}_3 \\
\text{HO} \\
\end{array}
\end{align*}
\]

Synthetic Drugs - drug molecules produced in a laboratory

\[
\begin{align*}
\text{morphine} & \xrightarrow{\text{H}_3\text{C}-\text{O}-\text{O}-\text{CH}_3} \text{heroin} \\
\text{heroin} & : \begin{array}{c}
\text{O} \\
\text{O} \\
\text{H}_3\text{C}-\text{C-O} \\
\text{N-CH}_3 \\
\end{array}
\end{align*}
\]
Spirituality and the Molecular World

390 septillion universes in a glass of water
Drug Administration

Drug Travels to Brain via Blood

Drug Crosses Blood Brain Barrier

Drug Accumulates in Reward Center

Drug Crosses Blood Brain Barrier

Increased Dopamine Causing Pleasure

Dopamine

nucleus accumbens
dorsal striatum
thalamus (purple)
How Does Dopamine Function in the Reward System?

Dopamine functions as a neurotransmitter. It allows for brain cells to communicate. It is released from one neuron into the synapse and attaches to a receptor on another neuron causing excitation (pleasure).
How does cocaine increase dopamine in the synapse?

1. Synthesis
2. Storage
3. Release
4. Binding
5. Reuptake Blocked

The result is more dopamine is in the synapse creating enhanced pleasure

http://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_par/i_03_m_par_cocaine.swf
How does heroin increase dopamine in the synapse?
Natural Rewards Elevate Dopamine Levels So That You Repeat Those Acts for Survival of the Species

Drugs of Abuse Cause a Dramatic Release of Dopamine

**AMPHETAMINE**
- **Accumbens**: Peak release at 1 hour, decreasing over 5 hours.
- **DA, DOPAC, HVA** levels shown in graph.

**COCAINE**
- **Accumbens**: Peak release at 2 hours, decreasing over 5 hours.
- **DA, DOPAC, HVA** levels shown in graph.

**NICOTINE**
- **Accumbens, Caudate**: Peak release at 1 hour, decreasing over 3 hours.

**MORPHINE**
- **Accumbens**: Release levels at different doses (0.5, 1.0, 2.5, 10 mg/kg) shown over 5 hours.

Source: Di Chiara and Imperato
PART IV - BRAIN IMAGING: PET SCANS

How do You Know where Dopamine Acts in the Brain?

• Ideally if dopamine could light up in the brain you could map where the light is in the brain and prove where dopamine acts.

• This technology has been achieved and is called Positron Emission Tomography (PET).

• PET is based on the use of a radiotracer called $^{11}$C-raclopride that binds to the dopamine receptor and emits light which leads to a PET Scan.
Positron Emission Tomography (PET)

(1) Inject radioactive raclopride.

(2) Raclopride travels through the blood stream into the brain and binds to dopamine receptors in the reward system.

(3) The patient is placed under a detector to detect the light given off by Raclopride.

(4) Since raclopride binds to dopamine receptors the light given off is in areas where there are dopamine receptors.
How is light emitted from a molecule of [C-11]-raclopride?

www.triumf.ca/welcome/petscan.html

alexteoh.com
Proof that methylphenidate increases the amount of dopamine in the synapse in the nucleus accumbens and ventral tegmental areas using brain imaging.

Volkow et. Al. JPET 291(1): 409-415, 1999
The Logic of a PET Scan

• The more raclopride in the brain the more red the color of the image because raclopride is bonding to the dopamine Receptors.

• If the dopamine receptors are already occupied with dopamine there will be no space for raclopride to bind and the brain image will show a yellow color (less raclopride present).

• Test
Which image has more raclopride bound to the dopamine receptor?
Which image has more dopamine bound to the receptor?
Which image is a brain under the influence of cocaine + raclopride?
PART V - BRAIN CHANGES IN COCAINE ADDICTION

CHANGES TO THE REWARD CENTER

Question 1:

Is there a difference in the amount of dopamine released in the reward center of the brain between cocaine addicted individuals and non-abusers?

Experiment 1:

Compare the changes in dopamine levels and the drug behavior effects between 20 cocaine abusers and 20 controls (non-abusers) who were given intravenous (iv) methylphenidate or a placebo.
Result 1: Cocaine abusers showed decreased dopamine in the reward centers of the brain compared to controls when given intravenous methylphenidate.

Volkow et al. Nature 386, 830-833, 1997
Experiment 2:

Compare the self-reported levels of “being high” and “craving” on a scale from 1 to 10 between 20 cocaine abusers and 20 controls (non-abusers) who were given intravenous (iv) methylphenidate or a placebo.

Question 2:

Is there a difference in reported experience of “being high” and the feeling of “cravings” between cocaine addicted individuals and non-abusers?
Self Reports of “Being High” and “Cravings” After Intravenous Methylphenidate in Controls and In Cocaine Abusers

Result 2: Cocaine abusers showed decreased drug induced rewards (high) and enhanced drug craving compared to controls

Volkow et. al. Nature 386, 830-833, 1997
Importance of These Results to Your Clinical Practice

• This result explains the reason for tolerance (a reduced response to drug’s action leading to a need for higher and higher doses of the drug to produce the initial effect)

• Addicted individuals need to take more drug to experience the same surge in dopamine as control subjects.

• Decreased dopamine levels during a sober state may explain why many individuals feel “restless, irritable and discontent”
Pavlov’s Experiment

Global Question: Can, people, places and things get you high?

1. Before Conditioning
   Drug → High response

2. Before Conditioning
   Person Using → Don’t Feel High

3. During Conditioning
   Drug + Person Using → High response

4. After Conditioning
   Person Using → Feel High

Low Strength Conditioned Response

High Strength Conditioned Response

conditioned stimuli
Question 1:

Does a conditioned stimuli increase dopamine in the nucleus accumbens in cocaine addicted individuals?

Experiment 1:

View a neutral and a cocaine cue video and determine how it affects dopamine levels by analyzing binding of [C-11]raclopride.
Result 1: Viewing a video of cocaine scenes decreased specific binding of raclopride presumably from dopamine increases in the synapse.

Volkow et. al. *J. Neuroscience*, 2006
Importance of These Results to Your Clinical Practice

1. Provides biological proof that triggers (people, places and things) can cause biological effects in cocaine abusers by increasing dopamine in the nucleus accumbens. Increased strengths of conditioned responses!!

2. Provides biological proof why people feel high after being triggered.

3. Provides biological proof that after a trigger dopamine is high and eventually begins to decrease and clients begin craving dopamine and start drug seeking behavior which can lead to a relapse.

4. Normal stimuli (food, sex, security and relationships) are no longer satisfying often they give up these for the drug which produces a sharper increase in dopamine in their brains. Often there is drug sex pairing to further enhance the amount of dopamine release.

5. Clinical Implications: A trigger causes a change in brain chemistry that causes you to feel the high just as though you were using leading to the phenomena of craving. How you deal with this craving will determine if you relapse or not. Teaching clients in early recovery how to deal with the high caused by a spike in dopamine levels after a trigger is a fundamental challenge of your practice.
THE EFFECT ON THE NUMBER OF DOPAMINE RECEPTORS

Question 1:

Are the number of dopamine receptors lower in cocaine addicts compared to normal individuals?

Experiment 1:

Analyze brain images of non-abusers and cocaine abusers in recovery after stopping cocaine use
Effect of Cocaine Abuse on Dopamine Receptors

Volkow et al. Synapse 14(2): 169-177, 1993

Result 1: Cocaine abusers showed lower dopamine receptors

Volkow et al. Synapse 14(2): 169-177, 1993
Dopamine D2 Receptors are Lower in Addiction

Cocaine

Meth

Alcohol

Heroin

Reward Circuits

Non-Drug Abuser

Drug Abuser

Dopamine D2 Receptors are Lower in Addiction

Volkow et. al. (2004)
Neurobiology of Learning and Memory 78, 610-624
Changed Set-Point Model of Addiction

• Neurons in the ventral tegmental area are set to release enough dopamine in the nucleus accumbens to provide a normal level of pleasure.

• After prolonged cocaine use the set point is changed such that the release of dopamine is reduced when normal pleasurable actions occur without cocaine (or heroin).

http://www.postregister.com/special/ofmethandmotherhood/part1_s12.php

# Importance of These Results to Your Clinical Practice

Abnormal Pleasure Seeking Behaviors To Compensate for Lower Dopamine Receptors Especially After Stopping Drug Use

<table>
<thead>
<tr>
<th>INSTINCT</th>
<th>NORMAL BEHAVIOR</th>
<th>ADDICTIVE BEHAVIOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEX</strong></td>
<td>Reproduction</td>
<td>Promiscuous sex,*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Masturbation and other bodily stimulation</td>
</tr>
<tr>
<td><strong>FOOD</strong></td>
<td>Eat when hungry</td>
<td>Eat excessively for the pleasant taste of food. Sweets, foods with a fatty texture.</td>
</tr>
<tr>
<td><strong>FRIENDSHIP</strong></td>
<td>Companionship (for reproduction and raising kids)</td>
<td>Unhealthy relationships</td>
</tr>
<tr>
<td><strong>SECURITY</strong></td>
<td>Moderate gain in wealth</td>
<td>Excessive gambling and shopping</td>
</tr>
</tbody>
</table>

*In many instance clients cannot distinguish the sex urge from the drug urge*
What is Known

- Frontal cortex allows you to change your behavior as a function of the reinforcer.

- Animals will press a lever to get food as long as food comes out of a hole.

- However, if they press a lever and food stops coming out then they stop pressing the lever.

- Animals with a damaged orbital frontal cortex keep pressing a lever even if food don’t come out. They lose their ability to stop.

Could the inability to stop taking cocaine be caused by damage to the orbital frontal cortex?
Question 1:

Do substance abusers show damage to the orbital frontal cortex?

Experiment 1:

Analyze glucose metabolism in the orbital frontal cortex (OFC) in substance abusers. Note: Glucose metabolism is a measure of the functioning of cells in the OFC.
Brain Glucose Metabolism in the Orbital Frontal Cortex of Cocaine Abusers and Controls

Result 1: Cocaine abusers showed decreased activity in the cingulate gyrus and orbital frontal cortex responsible for control.

CG = cingulate gyrus
OFC = orbital frontal cortex

Volkow et. al. AIP 156: 19-26, 1999
Importance of These Results to Your Clinical Practice

- These results demonstrate the activity of the orbital frontal cortex (the area of the brain responsible for control) has been altered due to cocaine abuse.
- Individuals with SUDs are fixated on using drugs despite negative reinforcers (jails, institutions, unemployment, homelessness).
- They may continue to use drugs because of damage in these areas similar to laboratory animals with damaged orbital frontal cortexes that continue to press a lever when no food is delivered.
PART VI – MODEL OF ADDICTION

Circuits Involved In Drug Abuse and Addiction

All of these brain regions must be considered in developing strategies to effectively treat addiction.
• Low numbers of dopamine receptors in the reward centers of the brain are found in people with addictions. These individuals do not experience the same pleasure as control groups with food, sex and other salient rewards and may seek out drugs to more efficiently stimulate their reward center.

• Individuals with low dopamine receptors in the reward centers have low metabolic activity in the orbital frontal cortex responsible for behavioral control which may contribute to an inability to stop using drugs despite negative consequences.

• Phenomena of Craving is Cue Induced: Increased strength of conditioned responses. Drug use impacts memory and learning. Surges in dopamine with drug cues causes cravings placing an individual at very high risk for relapse.
FMRI, works by detecting changes in blood oxygen levels and flow that occur in response to brain region activity.

When a brain area is more active it consumes more oxygen. To meet this increased demand, blood flow increases to the active area.

In the simplest fMRI experiment, a patient lies in an MRI scanner and watches a screen with images that alternate between showing a visual stimulus and a dark screen every 30 seconds. Blood flow increases in different brain areas during the visual stimulus which is detected.
Sexual Image And Drug Craving Signals Linked

Different Regions of the Brain Activated Drug Craving Self-Reports among Heroin Dependents

RED = desire and intention to use
BLUE = need for drug use
GREEN = drug use imagination
YELLOW = negative affect

Dysfunctional Default Mode Network in Methadone Treated Patients Who Have a Higher Heroin Relapse Risk

PART VIII - NEUROBIOLOGY INFORMED TREATMENT

- Medications that reduce drug cravings (buprenorphine, naltrexone, methadone) can prevent relapse while the brain is healing and normal emotional and decision making capacities are being restored.

**Brain Regions that Respond to Cues Before Naltrexone Injections**

**Brain Regions that Respond to Cues After Naltrexone Injections**

• Strengthen “natural reinforcers” to compensate for low dopamine receptors
  • Healthy eating
  • Exercise
  • Healthy Relationships

• Motivational Interviewing and Motivational Incentives for healthy stimulation of the reward center

Greater response in the parietal lobe during closed questions versus complex reflective questions asked by a therapist was significantly associated with less post-treatment drinking.
• **Neurofeedback (Voluntary Control of Brain Circuitry)**

People can voluntarily regulate brain activity in key areas of the reward center by simply conjuring up pleasurable imagery.

![Positive Neurofeedback with and without](image)


**Mindfulness Meditation**

![Mindfulness Meditation Baseline and Meditating](image)

(Harvard University (2011))
• Virtual Reality
CONCLUSIONS

(1) Brain imaging was used to show that addiction is a brain disease and not simply a failure of free will.

(2) The “powerlessness” experienced by many individuals with substance use disorders has a biological basis and may be related to damage to the orbital frontal cortex.

(3) The restless, irritable and discontented symptoms of alcoholism and other addictions observed by Dr. Silkworth in the book Alcoholics Anonymous in 1939 may be related to decreased dopamine receptors in the reward center of the brain elucidated by modern day brain imaging techniques.

(4) The phenomena of craving is due to increased strength of conditioned responses (cue-induced) and stress reactivity.